OIPE JC19
NOV 15 2004
PATENT & TRADEMARK OFFICE

AF IFW

THE UNITED STATES PATENT AND TRADEMARK OFFICE
Re: Appeal to the Board of Appeals

In re Application of	)	**MAIL STOP AF**
GARCIA-LADONA et al.	)	Art Unit: 1646
Serial No. 09/869,814	)	Examiner: Jiang
Filed: July 5, 2001	)	

For: BINDING PARTNERS FOR 5-HT5 RECEPTORS FOR MIGRAINE TREATMENT

To: Hon. Commissioner of Patents and Trademarks

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, PO Box 1450, Alexandria, VA 22313-1450, on: November 12, 2004
Date of Deposit
Karen Stamper
Person Making Deposit
Karen Stamper
Signature
November 12, 2004
Date of Signature

1. [ ] NOTICE OF APPEAL: Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Primary Examiner finally rejecting claims __.
2. [X] Please charge the amount of $430.00 to Dep. Acct. 11-0345 to cover the required extension of time fee.
3. [X] BRIEF on appeal in this application is transmitted herewith.
4. [ ] An Oral Hearing is requested.
   [ ] The Oral Hearing fee of $290.00 is enclosed.
5. [X] Fee $330.00
   [X] Charge to Dep. Acct. 11-0345.
6. [X] The Commissioner is hereby authorized to charge any fees which may be further required, or credit any over payment to Account No. 11-0345. A duplicate copy of this sheet is attached.

Respectfully submitted,
KEIL & WEINKAUF

By_____
Melvin Goldstein
Reg. No. 41566

MG/kas

1350 Connecticut Avenue, N.W.
Washington, D.C. 20036
(202) 659-0100

O.I.P.E. JC16
NOV 15 2004
PATENT & TRADEMARK OFFICE

AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of	)	**MAIL STOP APPEAL BRIEF**
GARCIA-LADONA et al.	)	Art Unit: 1646
Serial No. 09/869,814	)	Examiner: Jiang
Filed: July 5, 2001	)	

For: BINDING PARTNERS FOR 5-HT5 RECEPTORS FOR MIGRAINE TREATMENT

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, PO Box 1450, Alexandria, VA 22313-1450, on:

November 12, 2004
Date of Deposit

Karen Stamper
Person Making Deposit

Karen Stamper
Signature

November 12, 2004
Date of Signature

Honorable Comm'r. of Patents
PO Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

This Appeal is from the Examiner's Final Rejection of February 25, 2004.

REAL PARTY IN INTEREST

The real party in interest is Abbott & Co. KG of Germany. An assignment document to record the change of ownership from Knoll Aktiengesellschaft to Abbott Laboratories GmbH is in preparation and will be filed in due course.

RELATED APPEALS AND INTERFERENCES

To appellants' knowledge and belief, there are no interferences or other appeals within the meaning of 37 CFR § 1.912(c).

11/16/2004 HDEMESS1 00000007 110345 09869814
01 FC:1402 340.00 DA

STATUS OF CLAIMS

The claims in the application are claims 29-36. All of the claims have been rejected under the first paragraph of 35 USC § 112 as being insufficiently enabled by the original specification.

STATUS OF AMENDMENTS

The claims have not been amended subsequent to final rejection.

SUMMARY OF INVENTION

The claims are drawn to a method of treating migrainous cerebrovascular disorders by administering to the subject in need thereof an effective amount of at least one binding partner for a 5-HT5-receptor whose binding affinity for the 5-HT5-receptor is at least ten times greater than its affinity for a 5-HT1D receptor. Various types of migrainous disorders are set forth in the specification and illustrated in claim 36.

The advantage of the here claimed invention utilizing the ratio of binding affinities recited in claim 29 is that it makes possible the treatment of migraine-like cerebrovascular disorders with adequate efficacy and fewer side effects than previous treatments.

ISSUES

Are claims 29-36 adequately enabled by the original specification?

GROUPING OF CLAIMS

The claims have not been argued separately.

ARGUMENT

The following legal authorities are relied on in the following arguments in the

order in which they are cited.

In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988);

University of Rochester v. G.D. Searle + Co., 69 USPQ2d 1886 (Fed. Cir. 2004);

In re Angstaadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (Fed. Cir. 1976);

Eli Lilly & Co. v. Barr Labs, Inc., 251 F.3d 955, 58 USPQ2d 1865 (Fed. Cir. 2001);

Enzo Biochem., Inc. v. Gen-Probe, Inc., 323 F.3d 956, 63 USPQ 1609 (Fed. Cir. 2002)

In re Dinh-Nguyen, 492 F.2d 856, 181 USPQ 46 (CCPA 1974);

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); and

Bundy, 642 F2d 430, 434, 209 USPQ 48, 52 (Fed. Cir. 1981).

The claims

Claim 29 is the broadest claim and sets forth the critical binding affinities for the compounds used in the method with respect to the 5-HT5-receptor and the 5-HT1D-receptor, i.e., the binding affinity for the former must be at least ten times greater than the binding affinity for the latter.

A publication of Read et al., *Migraine & Headache Pathophysiology*, "Cortical spreading depression and migraine," pp. 81-92, 1999, has been made of record by appellants. That article showed that changes in metabolic, vascular and gene expression observed in experimental cortical spreading depression are complex and have a number of correlates in the clinic in migraine with or without aura (see page 89 under "Conclusions").

Retinal spreading depression is analogous to cortical spreading depression as

stated in a declaration of Dr. Garcia-Ladona of record as illustrated by another publication of record, DeLima et al., *Brain Research*, 614, pp. 45-51, 1993.

The examiner in the final rejection acknowledged that spreading despression is associated with migraine aura and may play a role in triggering classical migraine. Thus, certain aspects of the publications and declaration made of record by appellants do not appear to require any further discussion.

The basis for the rejection is that only a single compound, HK 02-01, has been shown to meet the binding affinity terms of the appealed claims, and that the Garcia-Ladona declaration of record only relates to the relative efficacy of that compound compared to the prior art compound sumatriptan. As support for this position, the examiner has relied on *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) and *University of Rochester v. G.D. Searle + Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004).

The examiner seems to base the rejection at least party on the assumption that the claimed method can be carried out only with either a 5-HT5 receptor agonist or a 5-HT5 receptor antagonist. This assumption, however, is not valid.

It is true that in principle one distinguishes between antagonist and agonistic effects that a drug may have on a particular receptor. However, this is only a rough classification. According to a more sophisticated (and realistic) view one has to differentiate between pure agonists, partial agonists, pure antagonists and partial antagonists (cf. the present specification on page 6, lines 23-26). To put it another way, any receptor agonist (perhaps with the exception of a 100% pure agonist) has a more

or less pronounced antagonistic effect on the receptor. This is why one and the same drug may even elicit opposite effects depending on the state of the subject treated. For instance, dihydroergotamin may cause a vasodilation in one patient and a vasoconstriction in another patient.

It should be emphasized in this connection that it is not required to know the effector function of the claimed 5-HT5 binding partners in order to carry out the invention. For instance, the Garcia-Ladona declaration shows that all the skilled person has to do is carry out the *in vitro* screening process and test the thus identified compounds in an appropriate animal model.

The screening process is set forth in the present application and enables the skilled person to read out those compounds which have the required binding affinity for a 5-HT5 receptor and selectivity over the 5-HT1D receptor. Appropriate animal tests are also set forth in the present application and enable the testing of the resulting compounds in terms of antimigraine activity. All that is required for this screening and testing is routine experimentation. See *Wands*, *supra*.

Contrary to the examiner's allegation, merely binding of a compound to a receptor can be used to predict the biological effect of the compound. In the present case, for instance, there is evidence that the binding affinity for 5-HT5 receptor of a compound correlates with the efficacy of said compound in the treatment of migraine. That is to say, if one compares, for instance, the recommended therapeutic dose for known antimigraine drugs with their binding affinity for 5-HT5 receptor, it can be seen

that the therapeutic dose increases as the binding affinity decreases (R(+)-Lisurid: 0.075 mg/day; Dihydroergotamin: 3 mg/day; Methylsergid: 2-6 mg/day; Sumatriptan: 100 mg/day; the 5-HT5 binding affinities are given in example 2 of the specification). Please note that this comparison does not belong to the prior art but is based on the present invention.

In vitro and *in vivo* methods have been fully set out in the present specification as alluded to above, and it would not be difficult or require undue experimentation on the part of one skilled in the art to identify suitable compounds without the use of undue experimentation. This is set forth in the *Wands* decision cited by the examiner and in *In re Angstaadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (Fed. Cir. 1976). Also see MPEP §§ 2164.01 and 2164.06.

The claims in US 6,048,850, which was the subject of the *University of Rochester* case cited by the examiner, were drawn to a method for selectively inhibiting PGHS-2 activity by administering a compound that selectively inhibits activity of the PGHS-2 gene product. Thus, what was claimed was to use a compound having a certain effect in a method for achieving said effect. This is a circular statement.

In contrast, the claims in the present application are directed to a method for treating particular diseases, i.e., migrainous cerebrovascular diseases such as migraine. Thus, the subject matter of the present claims is not simply confined to selectively inhibiting 5-HT5 receptor activity by administering compounds that selectively inhibit activity of the 5-HT5 receptor. On the contrary, the present invention

teaches for the first time that cerebrovascular disorders such as migraine can be effectively treated with binding partners for the 5-HT5 receptor. Thus, it is the relationship between 5-HT5 binding affinity and the treatment of certain diseases which represent the contribution the present invention makes over the prior art.

The '850 patent, however, does not make such a contribution. Actually, the gist of the '850 patent is the cloning of the PGHS-2 gene and the provision of a screening method for identifying a compound that inhibits prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2).

Two prior decisions cited in *University of Rochester* reflect the fact that physical properties can give a precise definition and that the principle set forth in *Metcalfe* is still correct. They are *Eli Lilly & Co. v. Barr Labs, Inc.*, 251 F.3d 955, 58 USPQ2d 1865 (Fed. Cir. 2001) and *Enzo Biochem., Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 63 USPQ 1609 (Fed. Cir. 2002). Indeed, as held in *Enzo*, disclosure of a nucleic acid can support a claim to nucleic acids that hybridize to it (i.e., that have a certain binding affinity for it).

The present specification sets forward several "animal models [based] on mechanisms which can underlie the formation of migraine" disorders (p. 11, lines 28-30). These animal models include protein extravasation, distrubution of carotid blood flow, measurement of the nitroglycerin-induced c-fos gene expression and translocation, measurement of other trascription factors such as c-jun, zif268, or Homer gene isoforms, retinal spreading depression, and cortical spreading depression (see specification at p.7, lines 15-21 and p. 11, line 32, through page 12, line 20). These

animal models are described in detail in the prior art, and testing identified 5-HT5 binding partners using these models would be a matter of routine to the appropriately skilled artisan.

The specification contains assertions as to the efficacy of 5-HT5 binding partners in treating migraine disorders which must be taken as enabling in the absence of specific reasoning to the contrary. *In re Dinh-Nguyen*, 492 F.2d 856, 181 USPQ 46 (CCPA 1974); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The reasoning presented by the examiner does not account for all information available to one of skill in the art, and is not, therefore, sufficient to overcome the established presumption.

The Garcia-Ladona declaration of record demonstrates the efficacy of 5-HT5 binding partners of the appropriate binding affinities relative to 5-HT1D affinity. The declaration supports the presumption that one of ordinary skill in the art would be able to carry out the presently claimed invention based on the specification disclosure and knowledge already in the art. Although the present claims are drawn to a process, the decision in *In re Bundy*, 642 F2d 430, 434, 209 USPQ 48, 52 (Fed. Cir. 1981), is considered to be quite relevant to the present fact situation, especially the quotation which follows:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed

by the present claim in order to satisfy the how-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public.

CONCLUSION

For the foregoing reasons it is respectfully submitted that reversal of the examiner's rejection of claims 29-36 is in order.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,

KEIL & WEINKAUF

Melvin Goldstein
Reg. No. 41,560

1350 Connecticut Ave., N.W.
Washington, D.C. 20036
(202)659-0100

MG/kas

APPENDIX

1-28 (canceled)

29. (previously presented) A method for treating migrainous cerebrovascular disorders which comprises administering to a subject in need thereof an effective amount of at least one binding partner for a 5-HT5-receptor whose binding affinity for the 5-HT5-receptor is at least 10 times greater than its binding affinity for a 5-HT1D-receptor.

30. (previously presented) The method as claimed in claim 29, where the binding affinity of the binding partner for a 5-HT5-receptor is at least 20 times greater than its binding affinity for a 5-HT1D-receptor.

31. (previously presented) The method as claimed in claim 29, where the binding affinity of the binding partner for a 5-HT5-receptor is at least 50 times greater than its binding affinity for a 5-HT1D-receptor.

32. (previously presented) The method as claimed in claim 29, where the K_i value for binding of the binding partner to the 5-HT5-receptor is less than 10^{-8} M.

33. (canceled)

34. (previously presented) The method as claimed in claim 29, wherein the migrainous cerebrovascular disorder is migraine.

35. (previously presented) The method as claimed in claim 34, wherein the binding partner is administered when acute symptoms of migraine occur.

36. (previously presented) The method as claimed in claim 34, wherein the migraine is

a disorder selected from the group consisting of associated migraine, migraine equivalents, digestive migraine, ophthalmic migraine, ophthalmoplegic migraine, migraine rouge, cluster headache and cervical migraine.